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Authors

Hoekstra, Mary
Chen, Hao Yu
Rong, Jian
[et al.](#)

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Genome-wide association study highlights *APOH* as a novel locus for lipoprotein(a) levels

Mary Hoekstra^{1,2}, Hao Yu Chen^{1,2}, Jian Rong³, Line Dufresne², Jie Yao⁴, Xiuqing Guo⁴, Michael Y. Tsai⁵, Sotirios Tsimikas⁶, Wendy S. Post⁷, Ramachandran S. Vasan³, Jerome I. Rotter⁴, Martin G. Larson³, George Thanassoulis^{1,2,*}, James C. Engert^{1,2,8,*}

¹Division of Experimental Medicine, McGill University, Montreal, Quebec ²Preventive and Genomic Cardiology, McGill University Health Centre and Research Institute, Montreal, Quebec ³Boston University's and NHLBI's Framingham Heart Study, Boston, Massachusetts ⁴The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California ⁵Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota ⁶Division of Cardiovascular Medicine, Sulpizio Cardiovascular Center, University of California San Diego, La Jolla, California ⁷Division of Cardiology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland ⁸Department of Human Genetics, McGill University, Montreal, Quebec

Abstract

Objective: Lipoprotein(a) (Lp(a)) is an independent risk factor for cardiovascular diseases and plasma levels are primarily determined by variation at the *LPA* locus. We performed a genome-wide association study (GWAS) in the UK Biobank to determine whether additional loci influence Lp(a) levels.

Approach and Results: We included 293,274 White British individuals in the discovery analysis. Approximately 93,095,623 variants were tested for association with natural log-transformed Lp(a) levels using linear regression models adjusted for age, sex, genotype batch, and 20 principal components of genetic ancestry. After quality control, 131 independent variants were associated at genome-wide significance ($P < 5 \times 10^{-8}$). In addition to validating previous associations at *LPA*, *APOE*, and *CETP*, we identified a novel variant at the *APOH* locus, encoding

Corresponding authors: James C. Engert, PhD, McGill University Health Centre, 1001 Decarie Blvd., Room EM1.2218, Montreal, Quebec H4A 3J1, Canada, Phone: 1-514-934-1934 ext. 35325 | jamie.engert@mcgill.ca; George Thanassoulis, MD, MSc, McGill University Health Centre, 1001 Decarie Blvd., Room D05.5120, Montreal, Quebec H4A 3J1, Canada, Phone: 1-514-934-1934 ext. 35465 | george.thanassoulis@mcgill.ca.
*co-senior authors.

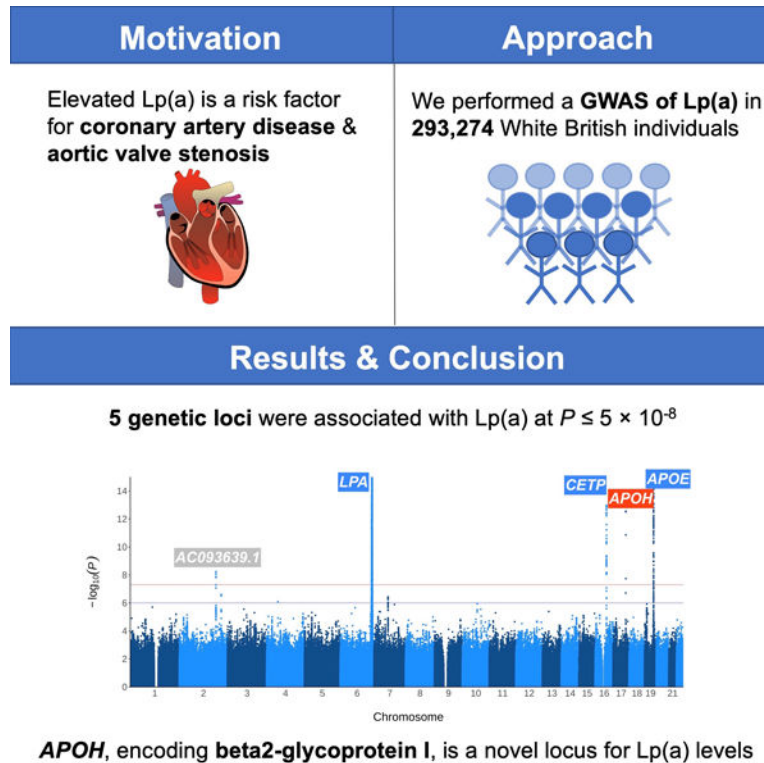
Disclosures

Dr Thanassoulis has participated in advisory boards for Amgen, Sanofi/Regeneron, Ionis, HLS Therapeutics, and Servier Canada and has received research grants from Ionis and Servier for research outside the scope of this work. Dr Tsimikas is a co-inventor and receives royalties from patents owned by UCSD on oxidation-specific antibodies and of biomarkers related to oxidized lipoproteins and is a co-founder and has an equity interest in Oxitope, Inc and its affiliates ("Oxitope") as well as in Kleanthi Diagnostics, LLC ("Kleanthi"). Although these relationships have been identified for conflict of interest management based on the overall scope of the project and its potential benefit to Oxitope and Kleanthi, the research findings included in this particular publication may not necessarily relate to the interests of Oxitope and Kleanthi. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

beta2-glycoprotein I (β 2GPI). The *APOH* variant rs8178824 was associated with increased Lp(a) levels (β [95% CI] (ln nmol/L), 0.064 [0.047, 0.081]; $P = 2.8 \times 10^{-13}$) and demonstrated a stronger effect after adjustment for variation at the *LPA* locus (β [95% CI] (ln nmol/L), 0.089 [0.076, 0.10]; $P = 3.8 \times 10^{-42}$). This association was replicated in a meta-analysis of 5,465 European-ancestry individuals from the Framingham Offspring Study and Multi-Ethnic Study of Atherosclerosis (β [95% CI] (ln mg/dL), 0.16 [0.044, 0.28]; $P = 0.0071$).

Conclusions: In a large-scale GWAS of Lp(a) levels, we identified *APOH* as a novel locus for Lp(a) in individuals of European ancestry. Additional studies are needed to determine the precise role of β 2GPI in influencing Lp(a) levels as well as its potential as a therapeutic target.

Graphical Abstract



Keywords

Lipoprotein(a); Lipids; Lipoproteins; GWAS

Subject codes:

Lipids and Cholesterol; Genetics; Genetic Association Studies

Introduction

Lipoprotein(a) (Lp[a]) is an independent risk factor for both coronary artery disease and aortic valve stenosis^{1,2}. Lp(a) consists of a low-density lipoprotein (LDL)-like particle

covalently bound to the glycoprotein apolipoprotein(a) (apo[a]). Levels of Lp(a) are primarily controlled by the size of the apo(a) protein, with smaller apo(a) isoforms leading to higher concentrations of plasma Lp(a). This size polymorphism is caused by a variable number of kringle IV type 2 repeats in the *LPA* gene. Together with other sequence variation in *LPA*, these kringle IV type 2 repeats are estimated to explain more than 90% of variability in Lp(a) concentration in individuals of European ancestry^{3,4}.

Lp(a) plasma concentrations vary widely between populations, with African-ancestry individuals having 2–3 fold higher levels than European-ancestry individuals^{5,6}. The distribution of Lp(a) is right-skewed across populations, with most individuals having very low levels⁷. While the precise physiological functions of Lp(a) are still unclear, there is evidence that it has proatherogenic and proinflammatory properties⁸. In pathophysiological studies, Lp(a) or apo(a) have been detected in both the lesioned intima of human arteries^{9–12} and in aortic valve lesions^{13,14}.

Several genome-wide association studies (GWAS) of Lp(a) have been performed, highlighting *LPA* as the major genetic determinant of Lp(a) levels^{4,7,15–20}. However, these studies have been limited by small sample sizes ($N < 15,000$), sparse genotyping arrays, or a focus on founder populations. In this study, we aimed to identify novel loci for Lp(a) by performing a GWAS in nearly 300,000 individuals from the UK Biobank. The findings could provide further insights into the regulation and clearance of Lp(a) particles and highlight novel targets for Lp(a)-lowering therapies.

Materials and Methods

The data that were analyzed for this study are available from the UK Biobank or from dbGAP in the case of the Multi-Ethnic Study of Atherosclerosis and the Framingham Offspring Study. For details, please see the Major Resources Table in the Supplemental Material.

Study Population

The UK Biobank study recruited over 500,000 individuals aged 40–69 years from 22 recruitment centers across the United Kingdom between 2006 and 2010. Participants provided blood samples for DNA extraction and biomarker analysis and completed a series of questionnaires, as previously described²¹. UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent. All relevant internal review boards approved this study. Only White British individuals were included in the discovery analysis to reduce confounding by ancestry, where White British ancestry was determined using a combination of self-reported ethnicity and results from a principal component analysis²¹.

Phenotyping

Lp(a) (nmol/L) was measured using an immunoturbidimetric analysis on a Randox AU5800. Measurements were taken at the initial assessment visit (2006–2010) or the first repeat assessment visit (2012–2013). Measurements that returned an error from the analyzer or

were outside of the reportable range (3.80–189 nmol/L) were excluded (n=91,426). Additional phenotypes are described in the Supplemental Material.

Genotyping

Genotyping was performed using the Affymetrix UK BiLEVE Axiom array on an initial 50,000 participants, while the remaining 450,000 participants were genotyped using the Affymetrix UK Biobank Axiom array. Quality control and imputation were performed centrally by the UK Biobank, as described previously²¹. Briefly, genetic markers were tested for batch effects, plate effects, departure from Hardy-Weinberg equilibrium, sex effects, array effects, and discordance across control replicates; markers that failed at least one test in a given batch had their genotype calls set to missing. Imputation was performed using only markers present on both the UK BiLEVE UK Biobank Axiom arrays, and markers that failed quality control in more than one batch, had a >5% missing rate, or had a minor allele frequency <0.0001 were removed. Samples with unusually high heterozygosity or >5% missing rate were excluded from analysis.

GWAS for Lp(a)

Associations of 93,095,623 genetic variants with natural log-transformed Lp(a) were tested in linear regression models assuming additive genetic effects in PLINK version 2.0^{22,23}. All models were adjusted for age, sex, genotype batch, and 20 principal components of ancestry. Variants with minor allele frequency <0.01 or imputation quality score <0.3 were removed (n=83,266,620). Clumping was performed on variants reaching genome-wide significance ($P < 5 \times 10^{-8}$) with PLINK version 1.9^{22,24}; index variants were chosen greedily starting with the lowest p-value, and variants less than 1Mb away from an index variant with an $r^2 > 0.01$ were assigned to that index variant's clump. The most significant independent variants in each locus (lead variants) were queried for previous associations using PhenoScanner (accessed 02/04/2020)^{25,26}. In a conditional analysis, all lead variants were tested for association with Lp(a) after additional adjustment for assessment center.

Conditional analysis of the *LPA* locus

A weighted *LPA*-region genetic risk score was created using all independent genome-wide significant variants in the *LPA* region. Lead variants outside the *LPA* region were tested for association with Lp(a) after adjusting for age, sex, genotype batch, 20 principal components, and the *LPA*-region genetic risk score.

Replication in Other Populations

The lead variant in each locus was tested for association with Lp(a) in other ethnic groups from the UK Biobank containing at least 1,000 unrelated individuals (South Asians, Black Africans, and Black Caribbeans). Lp(a) (nmol/L) was natural log-transformed and models were adjusted for age, sex, genotype batch, and 20 principal components. Lead variants were also assessed in a fixed-effects meta-analysis of self-reported White individuals from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Offspring Study. The variant rs1065853 was not available in these cohorts so rs7412 was used as a proxy (linkage

disequilibrium $r^2=0.99$ in the UK Biobank). Cohort descriptions and model details are provided in the Supplemental Material.

Statistical Analyses

Two-sided p-values $\leq 5 \times 10^{-8}$ were considered significant in the GWAS and two-sided p-values ≤ 0.05 were considered significant in all other analyses. Proportion of variance explained was calculated for independent significant variants in the *LPA* region independently, when modeled together, and when combined as a weighted genetic risk score.

Results

A total of 293,274 individuals with Lp(a) measurements were included in the study. Demographic characteristics of the UK Biobank Lp(a) subset are presented in Table I in the Supplemental Material, with individuals stratified by Lp(a) levels. Individuals with Lp(a) levels greater than or equal to the median were more likely to have coronary artery disease and aortic stenosis but were less likely to be female or diabetic (all $P < 0.001$). These individuals also had higher levels of LDL cholesterol (corrected and uncorrected for Lp[a]) and high-density lipoprotein cholesterol (all $P < 0.001$).

Following quality control, 9,829,003 variants with a minor allele frequency > 0.01 remained for further analysis. The association of these variants with Lp(a) showed no substantial inflation in the test statistics (genomic inflation factor $[\lambda] = 1.03$, Figure 1). After clumping, we identified 131 independent variants associated with Lp(a) at the genome-wide significance level of $P \leq 5 \times 10^{-8}$. The most significant variant, rs10455872 in *LPA*, explained 29% of variance in Lp(a) levels (Table II in Supplemental Material). There were 126 other independent variants in the *LPA* region, explaining an additional 20% of variance.

Outside the *LPA* region, we identified variants in four loci (Table 1). Variant rs1065853 on chromosome 19, located downstream of *APOE*, was associated with decreased Lp(a) levels (β [95% CI] (ln nmol/L), -0.11 [-0.12 , -0.10]; $P = 2.8 \times 10^{-96}$), as was variant rs247617 on chromosome 16, located upstream of *CETP* (β [95% CI] (ln nmol/L), -0.023 [-0.030 , -0.017]; $P = 1.0 \times 10^{-13}$). On chromosome 17, rs8178824 in *APOH* was associated with an increase in Lp(a) (β [95% CI] (ln nmol/L), 0.064 [0.047 , 0.081]; $P = 2.8 \times 10^{-13}$). Finally, variant rs826128 on chromosome 2, located in the long non-coding RNA *AC093639.1*, was associated with decreased Lp(a) levels (β [95% CI] (ln nmol/L), -0.039 [-0.053 , -0.026]; $P = 5.9 \times 10^{-9}$). The median Lp(a) level by genotype is shown for all lead variants in Table III of the Supplemental Material. Additional adjustment for assessment center did not materially change the results (Table IV in Supplemental Material).

The lead variant in each locus was evaluated for association with Lp(a) in the following populations from the UK Biobank: South Asian ($n=6,101$), Black African ($n=2,510$), and Black Caribbean ($n=3,207$). Consistent with results in White British individuals, rs10455872 was associated with increased Lp(a) in South Asians (β [95% CI] (ln nmol/L), 1.01 [$0.82, 1.19$]; $P = 8.5 \times 10^{-26}$) and Black Caribbeans (β [95% CI] (ln nmol/L), 0.81 [$0.59, 1.03$]; $P = 1.4 \times 10^{-12}$). This variant showed no association in Black Africans, likely owing to its low frequency in this population (minor allele frequency = 6.3×10^{-4}). The variant

rs1065853 near *APOE* was significantly associated with Lp(a) across ethnic groups, with Black African individuals demonstrating the largest decrease in levels per minor allele (T) (β [95% CI] (ln nmol/L), -0.28 [-0.34 , -0.21]; $P = 9.4 \times 10^{-16}$). The lead variants in *CETP*, *APOH*, and *AC093639.1* were not significantly associated in South Asians, Black Africans, or Black Caribbeans (Table V in Supplemental Material).

The lead variants were also tested for association with Lp(a) in a meta-analysis of 5,465 European-ancestry individuals from the Multi-Ethnic Study of Atherosclerosis and the Framingham Offspring Study. Both rs10455872 in *LPA* and rs8178824 in *APOH* were significantly associated with increased Lp(a) levels in the meta-analysis (rs10455872: β [95% CI] (ln mg/dL), 2.1 [2.0 , 2.2]; $P = 6.0 \times 10^{-534}$, and rs8178824: β [95% CI] (ln mg/dL), 0.16 [0.044 , 0.28]; $P = 0.0071$). The lead variants in *APOE*, *CETP*, and *AC093639.1* showed no significant effects (Table VI in Supplemental Material).

The weighted *LPA*-region genetic risk score contained 127 variants and explained 44% of the variance in Lp(a) levels. After adjusting for this score, variants in *APOE*, *CETP*, and *APOH* showed stronger effects on Lp(a) (Table VII in Supplemental Material). Conversely, the variant rs826128 on chromosome 2 showed a decreased effect and no longer reached genome-wide significance (β [95% CI] (ln nmol/L), -0.016 [-0.026 , -0.0058]; $P = 0.0019$).

Discussion

We performed a GWAS for plasma Lp(a) levels in 293,274 White British individuals from the UK Biobank. We confirmed the association of loci in the *LPA* region with Lp(a) levels, as well as *APOE* and *CETP*. In addition, we identified *APOH* as a novel risk locus and replicated this association in a meta-analysis of two independent cohorts.

As expected, our association study identified many significant variants in the *LPA* gene and the surrounding region. Despite imposing a stringent r^2 threshold (< 0.01), 127 variants were independently associated with Lp(a). Together, the top 4 variants explained 40% of the variance in Lp(a) levels, while the remaining 123 explained an additional 9%. Consistent with previous work^{1,20,27}, the variant rs10455872 was the most strongly associated with Lp(a), explaining 29% of variation in Lp(a) levels alone.

Outside of the *LPA* region, we identified variants at four loci, two of which have been previously associated with Lp(a) or Lp(a)-cholesterol: *APOE* and *CETP*. Our lead variant near the *APOE* locus, rs1065853, is in high linkage disequilibrium with the apoE2-defining variant rs7412 ($r^2=0.99$), which has been previously associated with decreased Lp(a)^{4,19,28,29}. Relative to the apoE3 and apoE4 isoforms, apoE2 has a lower affinity for LDL receptors and LDL receptor-related protein I, potentially leading to less competition for Lp(a) binding and greater clearance of Lp(a)³⁰. Upstream of the *CETP* locus, the variant rs247617 was also associated with decreased Lp(a) levels. This finding is consistent with clinical studies showing that inhibition of cholesteryl ester transfer protein, the product of *CETP*, decreases Lp(a) levels^{31–33}. This variant is also in high linkage disequilibrium with rs247616 ($r^2=0.99$), which has been previously associated with Lp(a)-cholesterol²⁸.

Apart from *APOE* and *CETP*, no other loci outside the *LPA* region have been associated with Lp(a) levels at the genome-wide significance level. Here, we identify rs8178824 in *APOH* as significantly associated with increased Lp(a) and provide independent replication. Relative to rs10455872, the effect size of rs8178824 is small, with individuals homozygous for the minor allele having a median Lp(a) level only 4.7 nmol/L higher than individuals with two major alleles. However, this effect is comparable to those seen for *APOE* and *CETP*, where the difference in homozygous genotype classes is 10.5 nmol/L and 1.9 nmol/L, respectively. As demonstrated previously with treatments targeting *CETP*, which produced reductions in Lp(a) of more than 30%^{31–33}, therapeutic targeting of the *APOH* locus could have a more substantial effect on Lp(a) than the effects of a single variant.

The *APOH* locus encodes beta2-glycoprotein I (β 2GPI), a single chain plasma protein with a high affinity for negatively charged surfaces³⁴. Recently, β 2GPI has been shown to interact with proprotein convertase subtilisin/kexin-9 (PCSK9)³⁵, whose inhibition leads to reductions in LDL cholesterol³⁶. This evidence is supported by previous studies demonstrating that genetic variation in *APOH* is associated with decreased levels of LDL cholesterol^{37–40} and peak particle diameter⁴¹. In vitro, β 2GPI has also been shown to bind to Lp(a), both through the phospholipids of the LDL component and through the kringle IV-domain of apo(a)⁴². Given that apo(a) is a major site for the accumulation of negatively charged oxidized phospholipids⁴³, the interaction of β 2GPI and Lp(a) may be primarily mediated through binding of β 2GPI to these phospholipids.

The variant we identified in *APOH* is in perfect linkage disequilibrium with rs1801689 ($r^2=1.0$). Interestingly, the amino acid change caused by rs1801689 (Cys325Gly, also known as Cys306Gly) has been shown to disrupt the ability of β 2GPI to bind to phospholipids⁴⁴. This change may reduce β 2GPI's affinity for oxidized phospholipids on apo(a), thereby allowing more free molecules of β 2GPI and Lp(a) to circulate in the plasma. Indeed, rs1801689 has also been previously associated with increased levels of plasma β 2GPI^{45,46}. The potential role of β 2GPI in lipid metabolism is further supported by the observation that it can accelerate triglyceride clearance in rats⁴⁷. Future studies should investigate whether the presence of β 2GPI similarly affects Lp(a) clearance or affects its pathogenicity through other mechanisms.

This study has several strengths and limitations. The UK Biobank discovery sample was larger than any previous Lp(a) GWAS, and thus had more power to detect novel associations. In addition, we were able to replicate our novel finding in *APOH* in a meta-analysis of two other European-ancestry cohorts. However, the *APOH* variant showed no association with Lp(a) in other ethnicities from the UK Biobank. The lack of replication observed for this variant and others may reflect reduced power due to smaller sample sizes, different allele frequencies, or different patterns of linkage disequilibrium⁴⁸; nonetheless, additional studies in larger non-European cohorts are warranted. Another limitation of our study is the high percentage of individuals missing Lp(a) measurements (>20%) in the UK Biobank due to the assay's limited reportable range (3.80–189 nmol/L); our results may therefore not apply to individuals with very high levels of Lp(a).

In summary, we have performed a large-scale GWAS of Lp(a) levels, validating previous loci and identifying *APOH* as a novel locus. Our findings provide further insight into the regulation of Lp(a) levels and highlight β 2GPI as a potential therapeutic target in individuals with elevated Lp(a).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

Lp(a)	Lipoprotein(a)
GWAS	Genome-wide association study
Apo(a)	Apolipoprotein(a)
LDL	Low-density lipoprotein
β2GPI	Beta2-glycoprotein I
MESA	Multi-Ethnic Study of Atherosclerosis

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Highlights

- We have performed a large-scale genome-wide association study of Lp(a) levels.
- We confirmed the association of variants in *LPA*, *APOE*, and *CETP* with Lp(a).
- We identified *APOH* as a novel risk locus for Lp(a), highlighting β 2GPI as a determinant of Lp(a) levels and a potential therapeutic target.

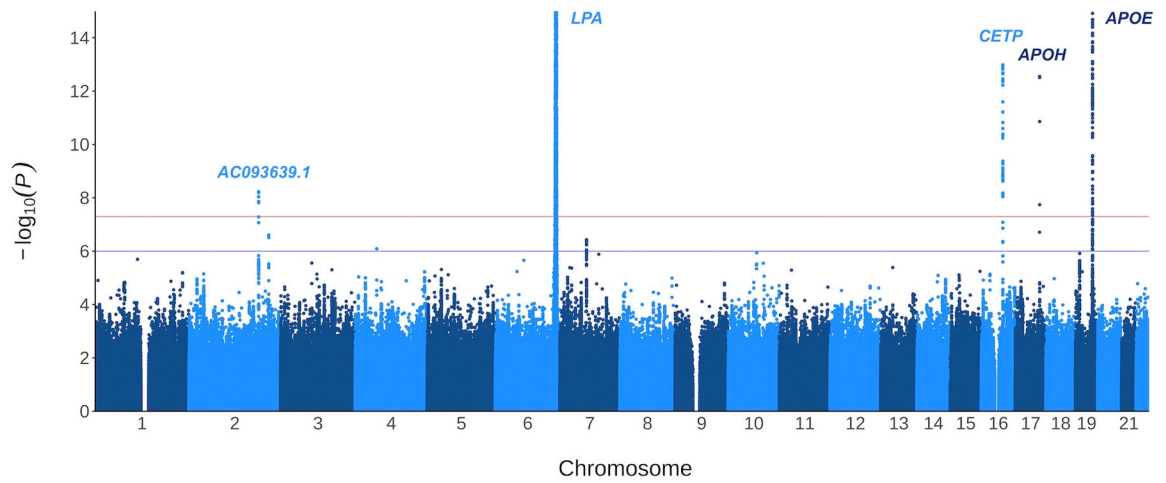


Figure 1:

Log-transformed p-values for the association of 9,829,003 variants with natural log-transformed Lp(a). The plot has been cropped for better resolution, truncating only the signals at chromosome 6 (*LPA* region) and chromosome 19 (*APOE* region).

Table 1:

Association of lead variants with Lp(a).

Variant	CHR	Position	Genes in Locus	Minor Allele (Freq)	β [95% CI] (ln nmol/L)	P	Variants in Locus*
rs10455872	6	161010118	<i>LPA, ZDHHC14, SNX9[†]</i>	G (0.076)	1.7 [1.7,1.7]	$6.2 \times 10^{-22,136}$	127
rs1065853	19	45413233	<i>APOE</i>	T (0.080)	-0.11 [-0.12, -0.10]	2.8×10^{-96}	1
rs247617	16	56990716	<i>CETP</i>	A (0.32)	-0.023 [-0.030, -0.017]	1.0×10^{-13}	1
rs8178824	17	64224775	<i>APOH</i>	T (0.030)	0.064 [0.047,0.081]	2.8×10^{-13}	1
rs826128	2	184797074	<i>AC093639.1</i>	A (0.054)	-0.039 [-0.053, -0.026]	5.9×10^{-9}	1

* Number of independent ($r^2 < 0.01$), genome-wide significant variants.

[†] Additional genes (+/- 3.5 MB from *LPA*): *TULP4, SYTL3, EZR, RPI-155D22.1, RSPH3, RPI-111C20.4, FNDC1, RPI1-125D12.1, RPI1-125D12.2, RP3-393E18.1, SOD2, ACAT2, PNLDCl, RPI-249F5.3, IGF2R, SLC22A1, SLC22A2, SLC22A3, LPAL2, PLG, RPI1-235G24.1, RPI1-235G24.2, RPI1-235G24.3, RP3-428L16.1, MAP3K4, AGPAT4, PARK2.*